REMARKS

Claims 37, 45 to 48, 53, 54, 72, and 75 to 78 and new Claim 80 are present for purposes of prosecution.

All of the above claims are rejected.

Reconsideration of the rejection of this application is respectfully requested in view of the above amendments and the following remarks.

Amendments to Claims

Independent Claims 37 and 72 have been amended to indicate that the metformin-glyburide combination is administered at a dosage of 250 mg metformin and 1.25 mg glyburide as set out in original Claim 50.

Applicant has amended the claims to indicate that the patients treated had no previous oral hyperglycemic treatment.

The term "drug naïve patient" refers to a patient who is to receive the drug as first line therapy for treatment of diabetes or related disease or condition as claimed herein. It would be apparent to those skilled in the art that the drug naïve patient does not refer to a patient who has never received any drug of any kind for any purpose. However, in order to make the claims more certain, the claims were previously amended to indicate that the drug naïve patient is a patient who has had no previous oral hyperglycemic treatment.

New Claim 80 has been added to cover subject matter in cancelled Claim 73.

Claim Rejections - 35 U.S.C. §112

All claims are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement.

The Examiner indicates that:

> "The claims in this application introduce new limitations into the instant invention, namely 'who has had no previous oral hyperglycemic treatment or has had no oral hypoglycemic treatment for 2 months' and 'at most 10% of the particles of the glyburide are greater than 46 μm'. The examiner determines that when all evidences in the original disclosure are considered and carefully reviewed, the newly amended claims fail to find support in the original specification.

> There is no express statement about such limitations that can be found in the specification. Particularly, the exclusion of patient population who 'has had no oral hyperglycemic treatment for 2 months' and the specific particle size distribution of '10% of the particles of the glyburide are less than 11 μm...46μm' recited in the present claims, which did not appear in the specification filed, introduces new concepts and violate the description requirement of the first paragraph of 35 USC 112."

The objected to phrase "has had no oral hyperglycemic treatment for 2 months" has been deleted from the claims.

In Claim 73, the specific particle size distribution of at most "10% of the particles of the glyburide are less than 11 μm . . . 46 μm" has been changed to at most "25% of the particles of the glyburide are less than 11 μm . . . 46 μm" as set out in the Specification at page 15, lines 21 to 25.

Discussion of Invention

Applicant's invention as claimed is defined as a method for

1) first line treatment of diabetes

2) in a drug naïve patient

3) wherein a low dose of a combination of metformin and glyburide (250 mg metformin and 1.25 mg glyburide) is administered

4) so that daily dosage of metformin is 750 mg or less, and

5) where the glyburide has a special particle size distribution of at most 25% of the particles are less than 11 μm and at most 25% are greater than 46 μm.

The essence of Applicant's method is to employ a maximum daily dosage of 750 mg metformin together with the glyburide of special particle size distribution to achieve equivalent efficacy as compared to efficacy achieved with prior art dosing that is more than 800 mg metformin/day, but with reduced side effects as compared to that observed with such prior art dosing. See page 41, lines 5 to 35 of the Specification.

In Applicant's method as claimed, use of the combination of the low dose formulation of metformin and glyburide in first line therapy (at most 750 mg/day metformin) is safer (less side effects) than the use of higher doses (greater than 800 mg/day metformin), without substantial loss in

efficacy. Applicant's invention as claimed resides in use of the low dose formulation of 250 mg metformin / 1.25 mg glyburide (to provide less than (or at most) 750 mg/day of metformin), in first line therapy, and which has essentially the same efficacy as the formulation containing 500 mg metformin / 2.5 mg glyburide (which provides more than 800 mg/day), but use of the low dose formulation results in reduced side effects. Please note Figures 9 and 10 which show that use of the combination of 250 mg metformin / 1.25 mg glyburide results in substantially reduced side effects as compared to use of 500 mg metformin / 1.25 mg glyburide. See Figures 1 to 8 wherein it is shown that the use of low dose of 250 mg metformin / 1.25 mg glyburide provides essentially the same efficacy as use of the dose of 500 mg metformin / 2.5 mg glyburide. As will be seen hereafter, with regard to Figures 1 to 10, where the low dose metformin (250 mg) of the invention is used, the daily amount of metformin is less than (or at most) 750 mg while where the high dose of metformin (500 mg) is used, the daily amount of metformin is greater than 800 mg (prior art). This clearly demonstrates that Applicant's method as claimed which employs a low dose formulation to provide a daily dosage of metformin of at most 750 mg is patentable over methods of treating diabetes with higher doses of metformin in combination with glyburide.

Please note page 11 of the Specification starting at line 34 and continuing to page 12, line 20:

> "In carrying out the method of the invention employing the preferred starting low dose pharmaceutical formulation containing metformin and glyburide, to treat drug naive patients for diabetes, the efficacy in treating drug naive patients is at least substantially equivalent and incidence of side effects (gastrointestinal side effects and hypoglycemia) is surprisingly significantly and substantially reduced as compared to patients on higher daily dosages of metformin and glyburide (that is in starting dosages prescribed in generally accepted medical practice for treating diabetes). Thus, while efficacy in treating drug naive patients as measured by decrease in hemoglobin A_{1c} (HbA_{1c}) from baseline over time, decrease in fasting plasma glucose (FPG), increase in post-prandial insulin levels, and decrease in post-prandial glucose (PPG) excursion, are essentially substantially equivalent in the above-described patients when employing the low dose pharmaceutical formulation employed herein and substantially higher daily dosages, incidence of hypoglycemia and gastrointestinal side effects in drug naive patients treated with substantially higher daily dosages are substantially greater than in patients treated with the low dose pharmaceutical formulation."

It is submitted that Applicant's method as claimed is patentable over the combination of the cited Barelli et al. patent and Bauer et al. patent.

Claim Rejections - 35 U.S.C. §103

All claims are rejected under 35 U.S.C. §103(a) as being unpatentable over Barelli et al. (WO 97/17975, pub. date: May 22, 1997, equivalent to US Patent 5,922,769) in view of Bauer et al. (US Patent 5,258,185, issue date: Nov. 2, 1993).

The Examiner contends in the rejection mailed January 17, 2007 that:

> "Claims 37, 45-54, 58-60, 71-73, and 75-79 are directed to a method of treating type 2 diabetes comprising administering to a drug naïve human patient, as first line therapy, a low dose of a combination of metformin and glyburide where the daily dosage of metformin is about 160 mg to about 750 mg; the daily dosage of glyburide is about 0.5 mg to 15 mg. Further limitations include: metformin and glyburide is formulated as a single dosage form (claim 45); weight ratio of metformin and glyburide is from about 400:1 to about 50:1 (claim 46); and that the glyburide having particular particle distributions and the patient population being drug naïve patients as recited in the claims."

> "Barelli et al. teach a combination of 500 mg metformin and 5 mg glibenclamide (glibenclamide and glyburide are synonymous) being useful for the treatment of type II diabetes (column 3, lines 14-17) and that the combination makes the therapeutical effect optimum at any time of the progression of the disease, starting from minor cases to the most severe ones (column 3, lines 19-21). Barelli et al. also disclose that the weight ratio of metformin and glibenclamide is 200:1 (column 2, lines 18-20) which overlaps with the claimed weight ratio. Barelli et al. further teach a single coated tablet in EXAMPLE 1 (column 9, lines 25-26) which contains 500 mg metformin and 5 mg glibenclamide."

The Examiner further states that:

> "The difference between Barelli et al.'s teaching and the instant claimed invention lies in that Barelli et al. do not teach (i) glyburide having particular particle distributions and (ii) the patient population being drug naïve patients."

Barelli does not teach or suggest employing low dose metformin (to provide a daily dose of metformin of at most 750 mg) which is the essence of Applicant's invention.

The Examiner further maintains that:

> "However, Bauer et al. teaches pharmaceutical formulations of glibenclamide rapidly releasing the active substance for the treatment of diabetes (see abstract). Bauer et al. disclose improved drug release and bioavailability (column 2, lines 17-22) of the drug glibenclamide by using a preparation having micronized glibenclamide with mean particle size of ±5 μm which overlaps with the instantly claimed particle size of 2-60 μm. Therefore, it would have been obvious to someone of ordinary skill in the art at the time of the instant invention to prepare micronized glibenclamide for the combination of metformin and glibenclamide as disclosed by

> Barelli et al. in view of Bauer et al. to result in the drug combination of the instant invention, motivated by Bauer et al. that glibenclamide is virtually water-insoluble (column 2, line 9) and micronized glibenclamide improves its solubility and bioavailability (column 2, lines 31-32). . . .
>
> "With respect to the recitation of metformin dosage being 250 mg, glyburide dosage being 1.25 mg of claims 50, 53, 54, 58, 59 and 79, although Barelli et al. do not explicitly teach this particular dosage, Barelli et al. have provided guidance that 1500 mg metformin and 15 mg glyburide are the maximum recommended daily dosage in the combination (column 3, lines 37-40) with recommended weight ratio of 200:1 (column 2, line 20) between metformin and glyburide. The determination of the appropriate dosage amounts of active ingredients for a treatment is routinely made by those of ordinary skill in the art and is well within the ability of tasks routinely performed by them without undue experimentation, especially in light of the dosage information of the active ingredient disclosed in the prior art. Thus, it would have been obvious to one of ordinary skill in the art at the time the instant invention was made to determine the amount of metformin and the amount of glyburide for achieving the effect of treating type 2 diabetes to result in the pharmaceutical composition as claimed with a reasonable expectation of success."

Barelli et al. disclose tablets containing a combination of 500 mg metformin and 5 mg glyburide for treating diabetes, so as to allow a daily dosage of 1500 mg metformin and 15 mg glyburide (column 2, lines 64 to 67). Barelli et al. teach that its tablets provide medicament for treating diabetes "in cases of secondary failure to a combination glibenclamide-metformin used in therapy [that is, 500 mg metformin / 2.5 mg glibenclamide or a ratio of 200:1 or 400 mg metformin / 2.5 mg glibenclamide or a ratio of 160:1]." The Barelli et al. combination is 500 mg metformin / 5 mg glibenclamide or a 100:1 ratio to achieve good efficacy with minimal side effects.

However, Barelli et al. has nothing to do with Applicant's inventive concept as claims.

1) The Barelli et al. combination is for patients who have previously failed on a combination of metformin and glyburide. Barelli et al. does not relate to first line treatment.

2) The patients employed in the Barelli study are not drug naïve patients as required in Applicant's method.

3) Applicant's method requires treating with a low dose combination of metformin (a maximum 750 mg daily) and glyburide.

4) Barelli et al. does not disclose or suggest using a low dose of metformin. Until Applicant's invention no one used a low dose of metformin, that is a maximum of 750 mg daily for

treatment of diabetes. It therefore has to be presumed that Barelli et al. is not implicitly or otherwise suggesting to use a low dose of metformin, that is 750 mg or less.

5) Barelli et al. makes no mention of particle size distribution of glyburide. Applicant's method requires a specific particle size distribution of glyburide not disclosed or suggested in Barelli et al.

Applicant has shown in working Example 3 that in accordance with the present invention use of a combination of 250 mg metformin and 1.25 mg glyburide to provide a metformin daily dose of less than 750 mg has reduced side effects and substantially equivalent efficacy as compared to a Barelli et al. combination of 500 mg metformin and 2.5 mg glyburide to provide a metformin daily dose of more than 800 mg. The fact that, in accordance with the present invention, use of a low dose combination of 250 mg metformin and 1.25 mg glyburide to provide a maximum daily dosage of 750 mg metformin has substantially equivalent efficacy of a Barelli et al.-like combination which provides a daily dosage of greater than 800 mg metformin, while causing reduced side effects as compared to the Barelli et al.-like combination is, indeed, surprising and unexpected.

As seen in Example 3, Applicant has compared efficacy and safety of a combination of 250 mg metformin / 1.25 mg glyburide to provide at most 750 mg metformin/day versus efficacy and safety of a combination of 500 mg metformin / 2.5 mg glyburide to provide more than 800 mg metformin per day. The glyburide used in both compositions is the specially sized glyburide as claimed. The key to the invention is use of the combination to provide at most 750 mg metformin per day. The results obtained, namely reduced side effects and substantially equivalent efficacy, is indeed surprising and unexpected. It is indeed unobvious that using a combination to provide less metformin (less than 750 mg/day) would provide substantially equivalent efficacy but reduced side effects as compared to using a combination to provide more metformin (greater than 800 mg/day). This is surprising and unexpected.

See pages 36 and 37 (Example 3) of the Specification wherein it is stated as follows:

"**RESULTS**

> The results obtained from the above studies indicate that the low dose metformin-glyburide (250/1.25) formulation of the invention achieved glycemic control at least essentially equivalent to the high dose metformin-glyburide (500/2.5) formulation as evidenced by

(1) a therapeutic response for hemoglobin A1c, namely, a reduction in HbA1c of below 7% (from a mean baseline of 8.2%) at week 20 (Figures 1, 2 and 3), at weeks 20 and 32 and final visit (Figures 4 and 5)

(2) a therapeutic response for fasting plasma glucose (FPG), namely, a reduction in FPG to less than 126 mg/dL after 20 weeks (from a baseline of about 175 mg/dL), (as shown in Figures 6)

(3) a therapeutic response for post-prandial insulin levels, namely an increase in post-prandial insulin of 19-25 μiu/mL (microinternational units/mL) (Figure 7)

(4) a therapeutic response for post-prandial glucose excursion (PPG) (that is the difference between post-prandial glucose and fast plasma glucose), namely, a decrease in post-prandial glucose excursion at week 20 of 17.7 for the 500/2.5 mg combo and 20.8 for the 250/1.25 mg combo versus 15.2 for metformin, 6.8 for glyburide. (Figures 8A and 8B).

At the same time, the above efficacy results employing the low dose formulation of the invention (Example 1) were achieved with reduced incidence of side effects (Figures 9 and 10).

As seen in Figure 9, the incidence of hypoglycemia employing the low dose formulation of the invention (Example 1) is less than about 1/3 of that occurring using the prior art high dose formulation (Example 2) employed in generally accepted medical practice for treating diabetes.

As seen in Figure 10, the incidence of gastrointestinal side effects employing the low dose formulation of the invention (Example 1) is less than 20% of that occurring using the high dose formulation (Example 2) employed in generally accepted medical practice for treating diabetes.

A discussion of the above results follows."

See pages 38 and 39 (Example 3) of the Specification wherein it is stated as follows:

"As first line therapy, a single formulation of fixed combination metformin/glyburide in ratio of a 200:1 metformin/glyburide was evaluated using two different dose strengths, a low dose (metformin/glyburide 250/1.25 mg) and a medium dose (metformin/glyburide 500/2.5 mg). The two dose strengths of fixed combination metformin/glyburide product were compared in a double-blind study to placebo, glyburide monotherapy and metformin monotherapy. Mean final doses achieved in each treatment arm were approximately 5.3 mg of glyburide [glyburide alone], 1307 mg of metformin [metformin alone], 557/2.78 mg [daily] of low dose (250/1.25 mg) metformin/glyburide fixed combination and 818/4.1 mg [daily] of

> medium dose (500/2.5 mg) fixed combination. When used as first line therapy, fixed combination metformin/glyburide treatment achieved statistically significant improvement in glycemic control compared to metformin, glyburide or placebo. The interim open-label treatment data confirmed the clinical utility of fixed combination therapy in a more 'glycemically diverse' patient population and for a longer period of time."

Thus, Applicant has presented comparative data which compares the formulation of the invention versus the closest prior art formulation.

In view of the above, it is quite clear that Applicant's method as claimed is neither disclosed nor suggested by Barelli et al. and thus is patentable over Barelli et al. and thus is patentable over Barelli et al.

It is submitted that Applicant's invention is claimed as patentable over Bauer et al.

U.S. Patent No. 5,258,185 to Bauer et al. discloses in Col. 2, lines 17 to 20,

> "microionized, i.e. finely comminuted, glibenclamide (mean particle size ±5 μm) showed an improved drug release and bioavailability above all in the presence of tensides . . ."

There is no disclosure or suggestion in Bauer et al. of a method of treating diabetes in a drug naïve patient employing a low dose of a combination of metformin and glyburide. Bauer et al. discloses formulations containing glyburide but not metformin. In addition, the glyburide employed in Applicant's invention as claimed will have a mean particle size greater than ±5 μm. Accordingly, it is clear that Applicant's invention as claimed is patentable over Bauer et al.

Applicant's method as claimed is also patentable over a combination of Barelli et al. and Bauer et al. As indicated, Barelli et al. does not disclose or suggest use of low dose metformin (160 to 750 mg daily) in drug naïve patients for first line therapy but only in secondary failure patients. Barelli et al. is devoid of Applicant's inventive concept of use of a combination of low dose metformin (maximum daily dosage of 750 mg) and specially size glyburide in first line treatment of drug naïve patients. Even if Barelli et al. is taken with Bauer et al. so that the Barelli et al. combination includes the Bauer et al. sized glyburide, the resulting combination would not make Applicant's method obvious since neither reference alone or in combination discloses or suggests use of low dose metformin (at most 750 mg/day) or treatment of drug naïve patients in first line therapy or use of specifically sized glyburide having a mean particle size of greater than ±5 μm.

The Examiner further maintains that:

> "Claims are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 23 and 44 of U.S. Patent No. 6,660,300 [to Timmins et al.]. Although the conflicting claims are not identical, they are not patentably distinct from each other because the patented invention makes obvious the instant invention."
>
> "The patented invention is directed to a method of administering the same combination of metformin and glyburide as that of the instantly claimed invention for treating diabetes which includes overlapping patient population of the type 2 diabetic patients in the instant invention. Therefore, the patented invention makes obvious the instant invention."

The Timmins et al. patent discloses and claims a biphasic controlled release delivery system for metformin alone or in combination with another pharmaceutical including glyburide. Timmins et al. in Claims 23 and 44 claim a combination of metformin and glyburide in the biphasic controlled release delivery system.

Timmins et al. does not disclose or suggest Applicant's inventive concept. There is no disclosure or suggestion in Timmins et al. of treating a drug naïve patient (first line therapy) with low dose metformin and specially sized glyburide as discussed above and as claimed herein. Accordingly, it is clear that Applicant's invention as claimed is patentable over Timmins et al.

In order to expedite prosecution of the subject application, Applicant submits herewith a terminal disclaimer in compliance with 37 C.F.R. §1.321(e) wherein the present application and U.S. Patent No. 6,660,300 are shown to be commonly owned and wherein Applicant disclaims the term of any patent issuing from the subject application which extends beyond the term of U.S. Patent No. 6,660,300

In view of the foregoing, it is submitted that Claims 37, 45 to 48, 53, 54 and 75 to 78 and 80 overcome all formal objections and are patentable over all cited art taken in any combination and therefore are in condition for allowance.

Respectfully submitted,

Bristol-Myers Squibb Company
Patent Department
P.O. Box 4000
Princeton, NJ 08543-4000
Phone: 609-252-4336
Date: December 19, 2007

/Burton Rodney, Reg. No. 22,076/
Burton Rodney
Attorney for Applicant